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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/674,228	09/29/2003	Samir M. Hanash	31755-A-PCT-USA-I	1891
38485	7590	02/12/2007		
ARENT FOX PLLC 1675 BROADWAY NEW YORK, NY 10019			EXAMINER REDDIG, PETER J	
			ART UNIT	PAPER NUMBER
			1642	
SHORTENED STATUTORY PERIOD OF RESPONSE		MAIL DATE	DELIVERY MODE	
3 MONTHS		02/12/2007	PAPER	

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary

Application No.

10/674,228

Applicant(s)

HANASH ET AL.

Examiner

Peter J. Reddig

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED, (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 07 December 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-4 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-4 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☐ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- ☐ Notice of Informal Patent Application (PTO-152)
- ☐ Other: _____

DETAILED ACTION

1. The Amendment filed December 7, 2006 in response to the Office Action of August 7, 2006 is acknowledged and has been entered. Previously pending claims 5-21 have been cancelled and claim 1 has been amended.
2. Claims 1-4 are currently being examined.
3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
4. The following rejections are being maintained:

Claim Rejections - 35 USC § 112

5. Claim 3 remains rejected under 35 USC 112 for the reasons previously set forth in section 6, pages 3-7 of the Office Action of August 7, 2006.

Applicant argues that (1) the references cited are old, they predate the application by at least 10-15 years and (2) much has been learned about cell cultures with numerous cell lines having been developed as surrogates for particular tumors in experimental study and the specification has provided one example of a cell line (SY5Y) that is representative of a certain type of tumor - neuroblastoma.

The argument has been considered but has not been found persuasive, (1') although applicant states that the references cited are old, the age of the references does not alter the relevance of those references and for the reasons of record, the claim is not enabled, (2') although applicant opines that in the intervening time, much has been learned about cell culture, with numerous cell lines having been developed as surrogates for particular tumors in experimental studies, it is noted that applicant is arguing limitations not recited in the claim as currently constituted. The claim is not drawn to surrogates, but rather to cell lines that are representative of the subject's tumor. Given the lack of definition of the term "representative" Examiner reasonably interpreted the term for examination purposes as "having the same characteristics as the subject's tumor cells". No objective evidence has been presented showing that the exemplified cell line has all of the same characteristics as any of the subject's tumor cells and given the known artifactual nature of cell lines, no one of ordinary skill in the art would believe it more likely than not that the cell culture cells in fact have all of the same

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characteristics as any of the subject's tumor cells and for the reasons previously set forth, the claim is not enabled.

Applicant argues that Examiner has explicitly acknowledged the existence of representative cell lines as surrogates for a patient's tumor in citing the 1988 paper of Hirsch et al. as anticipating the invention. The argument has been considered, but has not been found persuasive because, as drawn to the rejection under 35 USC 103, given the lack of definition of the term "representative" the Examiner reasonably interpreted the phrase "representative of the subject's tumor" as being "those cells used to isolate the proteins being subjected to two dimensional analysis ...from the same type of cancer cells" which is an assumption different from that drawn to the enablement rejection. Given the undefined nature of the term "representative" both interpretations of the term "representative" are reasonable and, for the reasons of record, the claim is not enabled.

Applicant argues that Schaadt et al teach that the L428 cell line is identical with that of freshly obtained Hodgkin (H) and Sternberg-Reed (SR) cells, except for the lack of Cig in the *in vitro* cells, which is explained by the culture conditions. The argument has been considered but has not been found persuasive since regardless of the differences in the exemplified cell line, the cell line is not "representative" of the subject's tumor.

Applicant argues that the inventors also set out in the Specification as filed that "it is also not necessary to utilize primary tissues, cells grown in culture may provide appropriate substitutes for tumor tissues or controls" (p8 lines 12-14). Applicant argues that in identifying proteins to which patients with a tumor produce a specific autoantibody response the source of the proteins is not limiting. Applicant argues that the specificity of the reaction is driven by the antibodies present in the sera, and in the ability to demonstrate a lack of antibodies with the same reactivity in the sera of patients without the tumor. Applicant argues that the inventors provide further guidance on the above on page 7 (lines 5-28) including, "The present invention is based on the discovery that serum from an individual that contains autoantibodies, such as a patient with cancer of the lung or neuroblastoma, can be used to identify protein antigens expressed in cells of a particular tissue, such as, for example, cells, of a tumor, or in a representative cell type to which the patient has autoantibodies." Applicant argues that thus, those of skill in the art would not consider it undue experimentation to identify representative cell lines.

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Applicant's argument has been considered but has not been found persuasive because, as stated above, given the lack of definition of the term "representative", Examiner reasonably interpreted the term for examination purposes as "having the same characteristics as the subject's tumor cells". Thus, whether or not the source of the protein is limiting for the reaction, the claim is not enabled because undue experimentation would be required of one of skill in the art to identify a cell line having the same characteristics as the subject's tumor cells for the reasons set forth in section 6, pages 3-7 of the Office Action of August 7, 2006.

Applicant's arguments have not been found persuasive and the rejection is maintained.

Claim Rejections - 35 USC § 103

6. Claims 1-4 remain rejected under 35 USC 103 for the reasons previously set forth in section 9, pages 10-13 of the Office Action of August 7, 2006

Applicants argue that, as admitted by the Examiner in the Office Action at page 12, lines 16-17, Hirsch et al. fail to teach the claimed invention and Kreskas et al. fail to add anything to the teachings of Hirsch et al. to render the claims obvious.

The argument has been considered but has not been found persuasive since applicant is arguing and discussing the references individually without clearly addressing the combined teachings. It must be remembered that the references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references, which made up the state of the art with regard to the claimed invention. Applicant's claimed invention fails to patentably distinguish over the state of the art represented by the cited references taken in combination for the reasons of record. In re Young, 403 F.2d 754, 159 USPQ 725 (CCPA 1968); In re Keller 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

Applicants further argue on p.11 of the Remarks of December 7, 2006 that:

i. Hirsch et al. fail to teach identification of a protein to which only a patient with cancer shows an autoimmune response because one control patient had antibodies against P-65.

Applicants argument has been considered, but has not been found persuasive because applicant is claiming limitations not recited in the claims as currently constituted because the claims are not drawn to identification of a protein to which **only** a patient with cancer shows an autoimmune response, but rather the claims as currently constituted, are drawn to "proteins bound by antibodies in the subject's serum but not the control serum". Given that the instant

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specification exemplifies only a single control serum for the disclosed example, it is clear that the claim for “the control serum” is a claim to a single control serum. Given that Hirsch et al. shows 34 controls, which do not present with the autoantibody, it is clear that Hirsch et al. shows a multiplicity of samples wherein “the control serum” does not have the autoantibodies.

ii. Hirsch et al. fail to teach identification of proteins to which patients with cancer raise an antibody response by performing 2D Western blot and comparing proteins to which antibodies in sera from patient with cancer react, whereas patients without cancer do not because the 2D analysis of Hirsch et al. used a pre-selected P-65 reactive patient and a known non-reactive control serum, Applicants point to page 205, col. 1, lines 13-15

Applicants' argument has been considered, but has not been found persuasive since applicant is arguing and discussing the references individually without clearly addressing the combined teachings. It must be remembered that the references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references, which made up the state of the art with regard to the claimed invention. Applicant's claimed invention fails to patentably distinguish over the state of the art represented by the cited references taken in combination. *In re Young*, 403 F.2d 754, 159 USPQ 725 (CCPA 1968); *In re Keller* 642 F.2d 413, 208 USPQ 871 (CCPA 1981). In particular, the combined references teach a method for identifying proteins, to which a subject produces autoantibodies consisting of the claimed method using the 2D electrophoresis and the steps/limitations of claims 1-4 wherein the combined references do not require pre-selection in order to determine protein differences. Furthermore, the Abstract of Hirsch et al. states the 1-D or 2-D gel electrophoresis was used and even if the paper is drawn to both, given the teachings of the combined references it would have been obvious to, and one would instantly envision and be able to, produce the claimed invention “consisting” of the claimed steps using 2-D electrophoresis alone given the clear teaching of the conventional and successful nature of the 2-D electrophoresis method by Krska et al in combination with the teachings of Hirsch et al. Further, one would clearly have a reasonable expectation of success using a non-preselected patient sera given that Hirsh et al identified the same protein bound by autoantibody in both unpreselected, that is the 1D, and the preselected 2D electrophoresis steps.

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iii. Hirsch et al, teach one of ordinary skill in the art away from the current invention by ignoring the multiple spots in the 2D gel electrophoresis Western blots of patients (fig 1A) and normal controls (fig 3A) which are dismissed as being "the usual background". Instead, Hirsch et al. teach that prior screening of sera using 1 D gel electrophoresis for discovery of autoantigens is necessary prior to 2D Western blotting.

Applicants' argument has been considered, but has not been found persuasive because it is well within the skill of those of ordinary skill in the art to recognize background noise in their experimental work. Additionally, as drawn to the screening of sera using 1 D gel electrophoresis, it is noted (as stated above) that it is the combinations of references that are relied upon and the combined references teach the claimed method as set forth above. Furthermore a review of Hirsch et al. did not reveal a single instance where the term "necessary" is used.

In regard to Krska et al. Applicants argue:

Krska et al merely describe a routine experiment to characterize a bacterial protein using monoclonal antibodies specific for the protein of interest. As such, it contributes no more than the inventor's own guidance as to the state of the art of 2D electrophoresis and Western blotting in the present specification. That Krska discloses a method of 2D Western blotting is not disputed, however it does not use a "signal-generating component bound to an antibody that is specific for antibodies, in the subject's sample" (emphasis added) of currently pending claim 4. Krska does not use antibodies specific for antibodies raised against an antigen extracted from a tumor cell or a tumor-derived cell line. Instead, they are detecting a hyperimmune monoclonal antibody raised through immunization with a purified bacterial protein. As such, Krska et al. is totally unrelated to the art of the current invention and is inappropriately combined with Hirsch et al.

Applicants' arguments have been considered, but have not been found persuasive because once again applicant is arguing and discussing the references individually without clearly addressing the combined teachings. It must be remembered that the references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references that made up the state of the art with regard to the

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claimed invention. Applicant's claimed invention fails to patentably distinguish over the state of the art represented by the cited references taken in combination. In re Young, 403 f.2d 754, 159 USPQ 725 (CCPA 1968); In re Keller 642 f.2d 413,208 USPQ 871 (CCPA 1981).

In particular, though Krska et al. is not drawn to the identification of proteins bound by cancer autoantibodies, Krska et al. teach the routine and conventional method at the time the invention was made of using 2D gels and Western blotting to identify a protein of interest bound by an antibody comprising using a signal-generating component bound to a second antibody that is specific for the primary antibodies used initially. Furthermore, contrary to Applicant's arguments, Hirsch et al. do indeed teach using rabbit anti-human IgG antibodies, which are specific for the antibodies in the Huntington's disease patient's sample; with the sequential addition of swine anti-rabbit IgG and PAP complex from rabbit to generate the immunoperoxidase reaction for signal generation to detect the proteins reactive with the autoantibodies.

Applicant argues that there is no teaching or suggestion to combine Hirsch et al. and Krska et al. The argument has been considered but has not been found persuasive because the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference and it is not that the claimed invention must be expressly suggested in any one or all of the references; but rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). In particular, Hirsch et al., teach a method of identifying proteins that induce autoantibodies in Hodgkin's disease which is a form of cancer, i.e. lymphoma, comprising the steps of isolating proteins from L428 cancer cells derived from Hodgkin's disease cancer patients, followed by subjecting isolated proteins to two-dimensional PAGE, followed by Western blot analysis with sera from cancer patients as compared to sera from normal control patients, wherein the proteins bound by antibodies present in the cancer patients serum but not the normal control serum are identified as proteins to which a subject with cancer produces autoantibodies, and detecting the proteins to which the autoantibodies in the subject's serum sample have bound with an antibody that is specific for autoantibody in the subjects sample, The teaching drawn to a method consisting-in-part of 2-D electrophoresis is further validated and suggested by Krska et al who teach the conventional 2-D

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electrophoresis method of detecting primary antibody bound to the antigen of interest for detection of proteins in 2D gel electrophoresis transferred to a membrane. Thus, the combined references provide not only the means, but also the motivation to make the claimed invention, that is to identify protein to which a subject with cancer produces autoantibodies as set forth in claims 1-4 and the invention is obvious for the reasons of record.

Applicant's arguments have been carefully considered, but have not been found persuasive and the rejection of claims 1-4 is maintained.

New Grounds of Objection

Specification

7. The amendment filed December 7, 2006 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material, which is not supported by the original disclosure, is as follows:

The statement "the disclosures of which are herein incorporated by reference in their entireties" adds new matter to the specification.

Applicant is required to cancel the new matter in the reply to this Office Action.

8. All other objections and rejections recited in August 7, 2006 are withdrawn.

9. No claims allowed.

10. This action is a **final rejection** and is intended to close the prosecution of this application. Applicant's reply under 37 CFR 1.113 to this action is limited either to an appeal to the Board of Patent Appeals and Interferences or to an amendment complying with the requirements set forth below.

If applicant should desire to appeal any rejection made by the Examiner, a Notice of Appeal must be filed within the period for reply identifying the rejected claim or claims appealed. The Notice of Appeal must be accompanied by the required appeal fee.

If applicant should desire to file an amendment, entry of a proposed amendment after final rejection cannot be made as a matter of right unless it merely cancels claims or complies with a formal requirement made earlier. Amendments touching the merits of the application

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which otherwise might not be proper may be admitted upon a showing a good and sufficient reasons why they are necessary and why they were not presented earlier.

A reply under 37 CFR 1.113 to a final rejection must include the appeal form, or cancellation of, each rejected claim. The filing of an amendment after final rejection, whether or not it is entered, does not stop the running of the statutory period for reply to the final rejection unless the Examiner holds the claims to be in condition for allowance. Accordingly, if a Notice of Appeal has not been filed properly within the period for reply, or any extension of this period obtained under either 37 CFR 1.136(a) or (b), the application will become abandoned.

11. Applicant's amendment necessitated the new grounds of objection, thus **THIS ACTION IS MADE FINAL**. Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. ' 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. ' 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

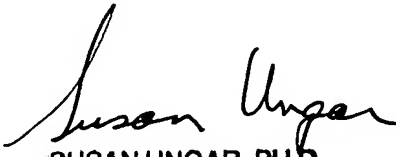
12. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Peter J. Reddig whose telephone number is (571) 272-9031. The Examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on (571) 272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

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system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



SUSAN UNGAR, PH.D.
PRIMARY EXAMINER

Peter J. Reddig, Ph.D.
Examiner
Art Unit 1642

PJR